Paul

Access DB# 97046

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: P Spivack Examiner #: 70400 Date: 6/18/03
Art Unit: 1614 Phone Number 30 84703 Serial Number: 09/940309
Mail Box and Bldg/Room Location: 2D01 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Tx of Movement Disorders

Inventors (please provide full names): Virginia Richter
Thomas Gidyz

Earliest Priority Filing Date: 9/15/99

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search methods of combating movement disorders* comprising administering a compound that is both a 5HT antagonist and an α_2 antagonist as, for example, mirtazapine.

*

AKA 6-aza mianserin

Thanks

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STAFF USE ONLY

Searcher: _____
Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: 6/19
Date Completed: 6/19
Searcher Prep & Review Time: 20
Clerical Prep Time: _____
Online Time: 51

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic _____
Litigation _____
Fulltext X
Patent Family _____
Other _____

Vendors and cost where applicable

STN 194.24
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (8-01)

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=> d que
L1          3339 SEA FILE=HCAPLUS ABB=ON  PLU=ON  5-HT ANTAGONISTS+OLD,NT/CT
L4           680 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ADRENOCEPTOR ANTAGONISTS (L)
                 .ALPHA.2-"+OLD/CT
L5         15772 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MOVEMENT DISORDERS+NT/CT
L7           338 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L1 OR (5HT? OR 5 HT?)(3A)(ANT
                 AG? OR INHIB? OR BLOCK?)) AND (L4 OR (.ALPHA.2 OR ALPHA2 OR
                 .ALPHA. 2 OR ALPHA 2)(3A)(ANTAG? OR INHIB? OR BLOCK?))
L8         32306 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 OR MOVEMENT(2A)(DISORDER
                 OR DISEASE) OR TREMOR? OR AKATHIS? OR ASTERIX? OR ATHETOS? OR
                 CHOREOATH? OR TICS OR CHOREA? OR DYSTON? OR SPASTIC? OR
                 RESTLESS LEGS OR HYPERKIN? OR HEMIBALL? OR MYOCLON? OR TARDIV?
                 OR PARKINSON? OR RUBRAL? OR TOURETTE?
L9            12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND L8


=> d ibib abs hitind l9 1-12

L9   ANSWER 1 OF 12  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2003:345983  HCAPLUS
TITLE:                   The .alpha.2-Adrenoceptor
                         Antagonist Idazoxan Reverses Catalepsy Induced
                         by Haloperidol in Rats Independent of Striatal
                         Dopamine Release: Role of Serotonergic Mechanisms
AUTHOR(S):               Invernizzi, Roberto W.; Garavaglia, Claudio; Samanin,
                         Rosario
CORPORATE SOURCE:        Istituto di Ricerche Farmacologiche Mario Negri',
                         Milan, Italy
SOURCE:                  Neuropsychopharmacology (2003), 28(5), 872-879
                         CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER:               Nature Publishing Group
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The .alpha.2-adrenoceptor antagonist
     idazoxan may improve motor symptoms in Parkinson's disease and
     exptl. Parkinsonism. We studied the effect of idazoxan on
     haloperidol-induced catalepsy in rats, an animal model of the drug-induced
     extrapyramidal side effects in man. Catalepsy was induced by a s.c.
     (s.c.) injection of haloperidol (1 mg/kg) and measured by the bar test for
     a max. of 5 min. At 3 h after haloperidol, rats were given 0.16-5.0 mg/kg
     s.c. idazoxan, and descent latency was measured 1 h later. Idazoxan
     potently reversed haloperidol-induced catalepsy with an ED50 of 0.25
     mg/kg. This effect was mimicked by the selective .alpha.
     2-adrenoceptor antagonist RS-15385-197 (0.3 and 1 mg/kg
     orally). We assessed how dopaminergic mechanisms were involved in the
     anticataleptic effect of idazoxan by studying its effect on dopamine (DA)
     release in the striatum, with the microdialysis technique in conscious
     rats. Idazoxan (0.3 and 2.5 mg/kg) had no effect on extracellular DA and
     did not modify the rise of extracellular DA induced by haloperidol,
     indicating that changes of striatal DA release were not involved in the
     reversal of catalepsy. The anticataleptic effect of 2.5 mg/kg idazoxan
     (haloperidol+vehicle 288.+-.8 s, haloperidol+idazoxan 47.+-.22 s) was
     attenuated in rats given an intraventricular injection of 150 .mu.g of the
     serotonin (5-HT) neurotoxin 5,7-dihydroxytryptamine (haloperidol+vehicle
     275.+-.25 s, haloperidol+idazoxan 137.+-.28 s). The 5-
     HT1A receptor antagonist WAY100 635 (0.1 mg/kg s.c.) did
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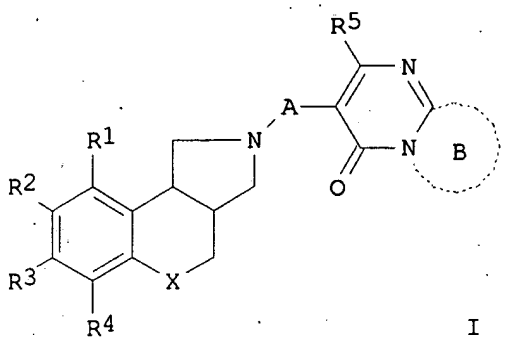
not affect the anticataleptic effect of idazoxan. The results suggest that idazoxan reversed haloperidol-induced catalepsy by a mechanism involving **blockade** of **.alpha.2**-adrenoceptors and, at least in part, 5-HT neurons.Neuropsychopharmacol. (2003) 28, 872-879, advance online publication, 19 Mar. 2003;.
CC 1 (Pharmacology)

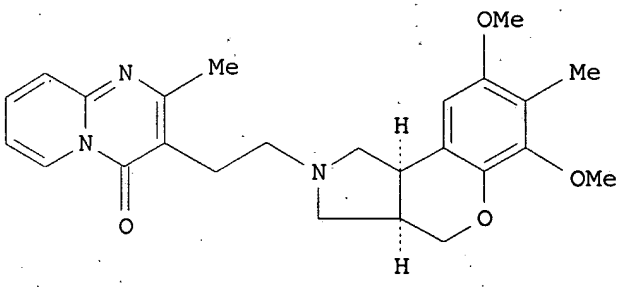
L9 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:155944 HCAPLUS
DOCUMENT NUMBER: 138:153545
TITLE: Preparation of pyrimidin-4-one derivatives, their pharmaceutical compositions and use as **.alpha .2/5-HT2c** double **antagonists**
INVENTOR(S): La Vielle, Gilbert; Dubuffet, Thierry; Muller, Olivier; Millan, Mark; Dekeyne, Anne; Brocco, Mauricette
PATENT ASSIGNEE(S): Les Laboratoires Servier, Fr.
SOURCE: Fr. Demande, 33 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2823752	A1	20021025	FR 2001-5216	20010418
EP 1256583	A1	20021113	EP 2002-290945	20020416
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NO 2002001806	A	20021021	NO 2002-1806	20020417
JP 2002356486	A2	20021213	JP 2002-114443	20020417
AU 2002034406	A5	20021024	AU 2002-34406	20020418
CN 1381456	A	20021127	CN 2002-116103	20020418
US 2003087916	A1	20030508	US 2002-125188	20020418

PRIORITY APPLN. INFO.: FR 2001-5216 A 20010418
OTHER SOURCE(S): MARPAT 138:153545
GI



I



II

AB Pyrimidin-4-ones (shown as I; variables defined below; e.g. 3-[2-[(3a.alpha.,9b.alpha.)-1,3a,4,11c-tetrahydrobenzo[5,6]chromeno[3,4-c]pyrrol-2(3H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one fumarate), their stereoisomers and addn. salts with pharmaceutically acceptable acids, pharmaceutical compns., methods of prepn. and uses as . **alpha.2/5-HT2c** double **antagonists** for the treatment of disorders such as depression, impulsive behavior, anxiety, schizophrenia, **Parkinson**'s disease, cognition disorder, libido disorder, sexual dysfunction, appetite disorder and sleep disorder are claimed. The above example I inhibits penile erection in rats induced by administration of a selective 5-HT2c agonist with ID50 = 2.6 mg/kg, s.c.; other test results are given for isolation-induced aggressiveness of mice, hiding of balls by mice, and affinity for .alpha.2 receptors of rats. One pharmaceutical compn. is tabulated. For I: R1, R2, R3 and R4 = H, halo, (C1-C6) linear or branched alkyl, (C1-C6) linear or branched alkoxy, (C1-C6) linear or branched polyhaloalkyl, hydroxy, cyano, nitro or amino, or R1 with R2, R2 with R3 or R3 with R4 together form, with atoms of C which carry them, an (un)substituted arom. or heteroarom. ring; X = O, methylene; A = (C1-C6) linear or branched alkylene chain; the B ring = unsatd. optionally substituted N heterocycle; R5 = (C1-C6) linear or branched alkyl; addnl. details are given in the claims. Seven example prepns. are included. For example, 3-[2-[(3a.alpha.,9b.alpha.)-6,8-dimethoxy-7-methyl-1,3a,4,9b-tetrahydrochromeno[3,4-c]pyrrol-2(3H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one sesquifumarate (base shown as II) was obtained starting from 2,4-dimethoxy-3-methylbenzaldehyde via intermediates 2,4-dimethoxy-3-methylphenol, 6,8-dimethoxy-7-methylcoumarin, (3.alpha.,4.alpha.)-1-benzyl-3-hydroxymethyl-4-(3,5-dimethoxy-2-hydroxy-4-tolyl)pyrrolidine, (3a.alpha.,9b.alpha.)-2-benzyl-6,8-dimethoxy-7-methyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole and (3a.alpha.,9b.alpha.)-6,8-dimethoxy-7-methyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole.

IC ICM C07D493-04
ICS A61K031-519; A61P025-16; A61P025-18; A61P025-22; A61P025-20
ICA C07D471-04; C07D239-00; C07D213-73
ICI C07D493-04, C07D311-00, C07D207-08
CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
ST pyrimidinone prepn **alpha2** adrenoceptor receptor **5HT2C** **antagonist**
IT **5-HT antagonists**
(**5-HT2C**; prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)
IT Mental disorder
(cognitive; prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)
IT Mental disorder
(depression; prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)
IT Appetite
Cognition
Sexual behavior
Sleep
(disorder; prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)
IT Drug delivery systems
(for pyrimidin-4-one derivs. as **.alpha.2/5-HT2c** double **antagonists**)
IT Behavior
(impulsive; prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)
IT Antidepressants
Antiparkinsonian agents
Antipsychotics
Anxiety
Anxiolytics
Cognition enhancers
Human
Parkinson's disease
Schizophrenia
(prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)
IT **Adrenoceptor antagonists**
(**.alpha.2-**; prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)
IT 496812-26-1P, 3-[2-[(3a.alpha.,9b.alpha.)-9-Methoxy-1,3a,4,9b-tetrahydrochromeno[3,4-c]pyrrol-2(3H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one dihydrochloride 496812-30-7P, 3-[2-[(3a.alpha.,9b.alpha.)-6,8-Dimethoxy-7-methyl-1,3a,4,9b-tetrahydrochromeno[3,4-c]pyrrol-2(3H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one sesquifumarate 496812-35-2P, 3-[2-[(3a.alpha.,9b.alpha.)-1,3a,4,11c-Tetrahydrobenzo[5,6]chromeno[3,4-

c]pyrrol-2(3H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one 496812-36-3P, 3-[2-[(3a.alpha.,9b.alpha.)-1,3a,4,11c-Tetrahydrobenzo[5,6]chromeno[3,4-c]pyrrol-2(3H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one fumarate 496812-39-6P, 6-[2-[(3a.alpha.,11c.alpha.)-1,3a,4,11c-Tetrahydrobenzo[5,6]chromeno[3,4-c]pyrrol-2(3H)-yl]ethyl]-7-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one fumarate 496812-41-0P, 3-[3-[(3a.alpha.,9b.alpha.)-1,3a,4,11c-Tetrahydrobenzo[5,6]chromeno[3,4-c]pyrrol-2(3H)-yl]propyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one hemifumarate 496812-45-4P, 3-[2-((3a.alpha.,11c.alpha.)-1,3,3a,4,5,11c-Hexahydro-2H-naphtho[1,2-e]isoindol-2-yl)ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one fumarate 496812-54-5P, 3-[2-[(3a.alpha.,9b.beta.)-6,8-Dimethoxy-7-methyl-1,3a,4,9b-tetrahydrochromeno[3,4-c]pyrrol-2(3H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one sesquifumarate 496812-57-8P, 3-[2-[(3a.alpha.,9b.alpha.)-9-Methoxy-1,3a,4,9b-tetrahydrochromeno[3,4-c]pyrrol-2(3H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)

IT 100-46-9, Benzylamine, reactions 140-88-5, Ethyl acrylate 922-67-8, Methyl propiolate 1592-38-7, Naphthalen-2-ylmethanol 4352-89-0, Benzo[f]chromen-3-one 7149-92-0, 2,4-Dimethoxy-3-methylbenzaldehyde 41078-70-0, 3-(2-Chloroethyl)-2-methylpyrido[1,2-a]pyrimidin-4-one 85995-45-5, Methyl cis-2,6-dimethoxycinnamate 86488-00-8, 6-(2-Chloroethyl)-7-methylthiazolo[3,2-a]pyrimidin-5-one 93102-05-7, N-Benzyl-N-(methoxymethyl)trimethylsilylmethylamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)

IT 778-48-3P, 2,3-Dihydro-4(1H)-phenanthrenone 782-28-5P, 4-(2-Naphthyl)butanoic acid 2506-41-4P, 2-Chloromethylnaphthalene 6326-90-5P, Ethyl 4-(2-naphthyl)butanoate 19676-67-6P, 2,4-Dimethoxy-3-methylphenol 175423-20-8P, (3a.alpha.,9b.alpha.)-2-Benzyl-9-hydroxy-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole hydrochloride 175423-21-9P, (3a.alpha.,9b.alpha.)-2-Benzyl-9-methoxy-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole hydrochloride 175423-73-1P, (3.alpha.,4.alpha.)-1-Benzyl-3-hydroxymethyl-4-(2,6-dimethoxyphenyl)pyrrolidine 208994-25-6P, (3a.alpha.,9b.alpha.)-9-Methoxy-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole 496812-27-2P, (3.alpha.,4.alpha.)-1-Benzyl-4-(2,6-dimethoxyphenyl)-3-pyrrolidinecarboxylate 496812-28-3P, (3.alpha.,4.alpha.)-1-Benzyl-3-hydroxymethyl-4-(2,6-dihydroxyphenyl)pyrrolidine 496812-31-8P, 6,8-Dimethoxy-7-methylcoumarin 496812-32-9P, (3.alpha.,4.alpha.)-1-Benzyl-3-hydroxymethyl-4-(3,5-dimethoxy-2-hydroxy-4-tolyl)pyrrolidine 496812-33-0P, (3a.alpha.,9b.alpha.)-2-Benzyl-6,8-dimethoxy-7-methyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole hydrochloride 496812-34-1P, (3a.alpha.,9b.alpha.)-6,8-Dimethoxy-7-methyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole 496812-37-4P, (3a.alpha.,11c.alpha.)-2,3,3a,11c-Tetrahydrobenzo[5,6]chromeno[3,4-c]pyrrol-4(1H)-one 496812-43-2P 496812-46-5P, Ethyl 4-(2-naphthyl)-2-butenoate 496812-47-6P, 1,2-Dihydro-4-phenanthrenecarbonitrile 496812-48-7P, 1,2,3,4-Tetrahydrophenanthrene-3,4-dicarbonitrile 496812-49-8P, 1,2,3,4-Tetrahydrophenanthrene-3,4-dicarboxylic acid 496812-50-1P,

(3a.alpha.,11c.alpha.)-3a,4,5,11c-Tetrahydrophenanthro[3,4-c]furan-1,3-dione 496812-51-2P, (3a.alpha.,11c.alpha.)-2-Benzyl-3a,4,5,11c-tetrahydro-1H-naphtho[1,2-e]isoindole-1,3(2H)-dione 496812-52-3P, (3a.alpha.,11c.alpha.)-2-Benzyl-2,3,3a,4,5,11c-hexahydro-1H-naphtho[1,2-e]isoindole 496812-55-6P, trans-3,5-Dimethoxy-6-hydroxy-4-methylcinnamic acid methyl ester 496812-56-7P, (3a.alpha.,9b.beta.)-2-Benzyl-6,8-dimethoxy-7-methyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole hydrochloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrimidinone derivs., their pharmaceutical compns. and use as **.alpha.2/5-HT2c** double **antagonists**)

L9 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:208109 HCAPLUS
DOCUMENT NUMBER: 134:231886
TITLE: Treatment of **movement disorders** by administration of 5-hydroxytryptamine receptor/. **alpha.2** adrenergic receptor **antagonist** compositions
INVENTOR(S): Richter, Virginia Pact; Giduz, Thomas
PATENT ASSIGNEE(S): Richter, Reed, USA; Hultquist, Steven J.
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019371	A1	20010322	WO 2000-US25380	20000915
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6281207	B1	20010828	US 1999-396335	19990915
EP 1223938	A1	20020724	EP 2000-965058	20000915
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003509371	T2	20030311	JP 2001-523003	20000915
US 2002035057	A1	20020321	US 2001-940309	20010827

PRIORITY APPLN. INFO.: US 1999-396335 A 19990915
WO 2000-US25380 W 20000915
OTHER SOURCE(S): MARPAT 134:231886
AB A method of combating **movement disorder** in a patient experiencing or susceptible to same involves administering to the patient an effective amt. of a neurotransmission modulating compn. including a **5-HT antagonist** and/or **.alpha.2 antagonist**. The antagonist may e.g. include a piperazinoazepine compd. such as mirtazapine that is a receptor

antagonist for **5-HT2**/3 and .alpha.2 receptors.
IC ICM A61K031-55
ICS A61K031-505; A61K031-44; A61K031-445; A61K031-415
CC 1-11 (Pharmacology)
ST **movement disorder** serotoninergic **alpha2** adrenergic **antagonist**
IT **5-HT antagonists**
Hyperkinesia
Movement disorders
Nervous system agents
Tremor
(**5-HT** receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT **5-HT antagonists**
(**5-HT2A**; **5-HT** receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT **5-HT antagonists**
(**5-HT3**; **5-HT** receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT Brain, disease
(Gilles de la **Tourette** syndrome, **tremor**; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT **Parkinson's disease**
(**Parkinsonian tremor**; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT Nervous system
(**akathisia**; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT Brain
(basal ganglia, impairment; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT Brain
(cerebellum, cerebellar **tremor**; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT Drugs
(drug-induced **tremor**; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT Nervous system
(dyskinesia; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT Nervous system
(**dystonia**; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)
IT Alkaloids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ergot; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Alkaloids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolealkylamine; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Muscle, disease
(**myoclonus**; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Heterocyclic compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrogen, tetracyclic; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Neurotransmission
(noradrenergic, modulating agents; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Drug delivery systems
(oral; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Nerve, disease
(peripheral neuropathy, **tremor** assocd. with; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Leg
(restless leg syndrome; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Mental activity
(sedation; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Neurotransmission
(serotoninergic, modulating agents; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Nervous system
(**spasticity**; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Nervous system
(**tardive** dyskinesia; 5-HT receptor/**.alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT Injury
(trauma, post-traumatic **tremor**; 5-HT receptor/**.alpha.**

2 adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT **Adrenoceptor antagonists**
(.**alpha.2**-; **5-HT** receptor/ .**alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT 60-79-7, Ergonovine 129-03-3, Cyproheptadine 361-37-5, Methysergide 5786-21-0, Clozapine 15574-96-6, Pizotifen 24219-97-4, Mianserin 28299-33-4D, Imidazoline, derivs. 74050-98-9, Ketanserin 79944-58-4, Idazoxan 81167-16-0, Imiloxan 85650-52-8, Mirtazapine 87051-43-2, Ritanserin 89565-68-4 89565-96-8 89566-10-9 99614-02-5, Ondansetron 104054-27-5, Atipamezole 106266-06-2, Risperidone 112727-80-7 113140-33-3 117844-17-4 124998-65-8 152148-90-8 152148-95-3 152149-09-2 152149-11-6 152149-13-8 152149-17-2 152149-33-2 152149-36-5 152150-77-1 152150-78-2 152150-79-3 152150-80-6 330195-80-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(5-HT receptor/.**alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

IT 59-92-7, Levodopa, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(dyskinesia induced by; 5-HT receptor/.**alpha.2** adrenergic receptor **antagonist** compns. for treatment of **movement disorders**)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:185043 HCAPLUS
DOCUMENT NUMBER: 134:217215
TITLE: Use of CRF antagonists and related compositions for modifying circadian rhythm and treatment of depression and other conditions
INVENTOR(S): Chen, Yuhpyng Liang
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1082960	A2	20010314	EP 2000-307074	20000818
EP 1082960	A3	20020320		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6432989	B1	20020813	US 2000-587007	20000605
JP 2001097889	A2	20010410	JP 2000-251836	20000823
NZ 506562	A	20020927	NZ 2000-506562	20000825
US 2002156089	A1	20021024	US 2002-161816	20020604

PRIORITY APPLN. INFO.: US 1999-151183P P 19990827
US 2000-587007 A3 20000605

AB A corticotropin releasing factor (CRF) antagonist is administered to treat disorders that can be treated by altering circadian rhythm, as well as depression (in which a second compd. for treating depression is administered, the second compd. having an onset of action that is delayed with respect to that of the CRF antagonist). Methods for treating cardiovascular diseases, migraine, non-migraine headaches, and emesis are also disclosed.

IC ICM A61K031-519
ICS A61K031-505; A61K031-522; A61K031-4427

CC 1-12 (Pharmacology)
Section cross-reference(s): 2, 63

IT **5-HT antagonists**
(**5-HT1A**; CRF **antagonists** and related compns. for modifying circadian rhythm and treatment of depression and other conditions, and use with other agents)

IT **5-HT** receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CRF **antagonists** and related compns. for modifying circadian rhythm and treatment of depression and other conditions, and use with other agents)

IT Leg
(**restless legs** syndrome; CRF antagonists and related compns. for modifying circadian rhythm and treatment of depression and other conditions, and use with other agents)

IT Adrenoceptor agonists
(.**alpha.2**-; CRF **antagonists** and related compns. for modifying circadian rhythm and treatment of depression and other conditions, and use with other agents)

L9 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:780858 HCAPLUS
DOCUMENT NUMBER: 130:119873
TITLE: Head and whole-body jerking in guinea pigs are differentially modulated by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists**
AUTHOR(S): Nielsen, Christina Kurre
CORPORATE SOURCE: Pharmacological Research, H. Lundbeck A/S, Copenhagen, DK-2500, Den.
SOURCE: European Journal of Pharmacology (1998), 361(2/3), 185-190
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study examd. the role of 5-hydroxytryptamine 5-HT receptor subtypes on 5-hydroxytryptamine- (5-HT-) mediated **myoclonus** in guinea pigs, evaluating head and whole-body jerking as two distinct behavioral responses. **Myoclonus** was induced by the 5-HT precursor l-5-hydroxytryptophan (l-5-HTP) and the non-selective 5-HT1A/1B/5-HT2 receptor agonist 5-methoxy-N,N-dimethyltryptamine (5-MeODMT). The selective **5-HT1A** receptor **antagonist** WAY100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride) inhibited both head and whole-body jerking. The selective **5-HT1B**/1D receptor **antagonist** GR127935 (N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-

1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide hemifumarate) only inhibited whole-body jerking, which resulted in unmasked head jerking. Co-administration of GR127935 and the selective **5-HT2A** receptor **antagonist** MDL100.151 ((.+-.)-.**alpha**.-(**2**,3-dimethoxyphenyl)-1-[-2-(4-fluorphenyl)ethyl]-4-piperidinmethanol) caused a complete inhibition of whole-body as well as head jerking. MDL100.151 had only limited effect on **myoclonic** jerking when given alone. The **inhibitory** effects of the **5-HT** receptor **antagonists** on either 1-**5-HTP**- or 5-MeODMT-induced **myoclonus** were found to be very similar. These data confirm a role for the 5-HT1A and 5-HT1B/1D receptors and suggest a role for 5-HT2A receptors in mediating **myoclonus** in guinea pigs. Moreover, the study shows that by considering head and whole-body jerking as two pharmacol. distinct behavioral responses, subtype specific 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** can be distinguished.

CC 2-8 (Mammalian Hormones)

ST serotonin S1A S1B S2A receptor head body jerking **myoclonus**

IT 5-HT receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(5-HT1A; head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)

IT 5-HT receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(5-HT1B; head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)

IT 5-HT receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(5-HT1D; head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)

IT 5-HT receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(5-HT2A; head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)

IT Behavior
(body jerking; head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)

IT Behavior
(head jerking; head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)

IT Muscle, disease
(**myoclonus**; head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)

IT 50-67-9, 5-Hydroxytryptamine, biological studies 1019-45-0, 5-Methoxy-N,N-dimethyltryptamine 4350-09-8, 5-Hydroxytryptophan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)
IT 139290-69-0, MDL100151 146714-97-8, WAY100635 148672-13-3, GR127935
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(head and whole-body jerking differential modulation by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** in guinea pig)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:426105 HCAPLUS
DOCUMENT NUMBER: 129:225564
TITLE: Characterization of enhanced behavioral responses to L-DOPA following repeated administration in the 6-hydroxydopamine-lesioned rat model of **Parkinson**'s disease
AUTHOR(S): Henry, Brian; Crossman, Alan R.; Brotchie, Jonathan M.
CORPORATE SOURCE: Manchester Movement Disorder Laboratory, Division of Neuroscience, School of Biological Sciences, University of Manchester, Manchester, M13 9PT, UK
SOURCE: Experimental Neurology (1998), 151(2), 334-342
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Long-term treatment of **Parkinson**'s disease with dopamine-replacing agents such as L-3,4-dihydroxy-phenylalanine (L-DOPA) is compromised by many side-effects, most notably involuntary movements, L-DOPA-induced dyskinesia. Acute challenge with dopamine-replacing drugs elicits a rotational response in the 6-hydroxydopamine (6-OHDA)-lesioned rat model of **Parkinson**'s disease. This rotation is contraversive to the lesion and is considered to represent an antiparkinsonian effect. More recently, it has become clear that the rotational response shows plasticity and that repeated L-DOPA or apomorphine therapy is accompanied by a marked enhancement in this response. In this study, the authors demonstrate that the enhanced behavioral response to repeated dopamine-replacement therapy seen in the 6-OHDA-lesioned rat has pharmacol. characteristics similar to L-DOPA-induced dyskinesia seen in MPTP-lesioned primates and man. Thus, the magnitude and rate of development of the enhanced response to L-DOPA treatment is related to both the no. of doses and the size of the dose of L-DOPA administered. In contrast, de novo administration of dopaminergic drugs that are assocd. with a lower incidence of dyskinesia, e.g., bromocriptine or lisuride, does not lead to an enhanced behavioral response following repeated treatment. However, following a single "priming" administration of apomorphine, the rotational response elicited by subsequent bromocriptine administrations is enhanced with repeated treatment. Once established, the enhanced behavioral response to repeated L-DOPA-administration (6.5 mg/kg, twice daily) can, like L-DOPA-induced dyskinesia in man and MPTP-treated monkeys, be selectively reduced by coadministration of L-DOPA with the **alpha2**-adrenergic receptor **antagonist** yohimbine (10 mg/kg, -95%), the **5-HT**

uptake **inhibitor** 5-MDOT (2 mg/kg, -90%), or the beta-adrenergic receptor antagonist propranolol (10 mg/kg, -35%). While these rats do not exhibit symptoms of dyskinesia per se, this rodent model does exhibit behaviors, the underlying mechanism of which is likely to be similar to that underlying L-DOPA-induced dyskinesia and may prove useful in studying the mol. and cellular mechanisms of L-DOPA-induced dyskinesia in **Parkinson**'s disease. (c) 1998 Academic Press.

CC 1-11 (Pharmacology)

ST behavior sensitization DOPA **parkinsonism** dyskinesia; dopaminergic drug behavior sensitization **parkinsonism** dyskinesia

IT Antiparkinsonian agents
Dopamine agonists
(characterization of enhanced behavioral responses to L-DOPA and other dopaminergic drugs following repeated administration in hydroxydopamine-lesioned rat model of **Parkinson**'s disease in relation to induction of dyskinesia)

IT Toxicity
(drug; characterization of enhanced behavioral responses to L-DOPA and other dopaminergic drugs following repeated administration in hydroxydopamine-lesioned rat model of **Parkinson**'s disease in relation to induction of dyskinesia)

IT Nervous system
(dyskinesia; characterization of enhanced behavioral responses to L-DOPA and other dopaminergic drugs following repeated administration in hydroxydopamine-lesioned rat model of **Parkinson**'s disease in relation to induction of dyskinesia)

IT Behavior
(rotational; characterization of enhanced behavioral responses to L-DOPA and other dopaminergic drugs following repeated administration in hydroxydopamine-lesioned rat model of **Parkinson**'s disease in relation to induction of dyskinesia)

IT Behavior
(sensitization; characterization of enhanced behavioral responses to L-DOPA and other dopaminergic drugs following repeated administration in hydroxydopamine-lesioned rat model of **Parkinson**'s disease in relation to induction of dyskinesia)

IT 58-00-4, Apomorphine 7101-51-1, L-DOPA methyl ester 19875-60-6 25614-03-3, Bromocriptine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of enhanced behavioral responses to L-DOPA and other dopaminergic drugs following repeated administration in hydroxydopamine-lesioned rat model of **Parkinson**'s disease in relation to induction of dyskinesia)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:646550 HCAPLUS
DOCUMENT NUMBER: 127:326359
TITLE: MK-801-induced hyperlocomotion: Differential effects of M100907, SDZ PSD 958 and raclopride
AUTHOR(S): Martin, Peter; Waters, Nicholas; Waters, Susanna; Carlsson, Arvid; Carlsson, Maria L.
CORPORATE SOURCE: Department of Pharmacology, Goeteborg University, Medicinaregatan 7, 90, Goteborg, S-413, Swed.

SOURCE: European Journal of Pharmacology (1997), 335(2/3), 107-116
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The influence of three selective monoamine receptor antagonists on spontaneous locomotion and on the hyperlocomotion induced by the un-competitive N-methyl-D-aspartate (NMDA) receptor antagonist [+]-5-methyl-10,11-dihydro-5H-dibenzo-[a,d]-cyclohepten-5,10-imine hydrogen maleate (MK-801; dizocilpine) was investigated. The selective and potent 5-hydroxytryptamine (**5-HT**)2A receptor **antagonist** R(+)-.**alpha**.(2,3-dimethoxyphenyl)-1-[2(4-fluorophenyl)ethyl)]-4-piperidine-methanol (MDL100,907; M100907) displayed a clear-cut selectivity for redn. of MK-801-induced as compared to spontaneous locomotion, in that the former was dose-dependently (0.001, 0.01, 0.1 mg/kg i.p.) blocked and even totally abolished by the highest dose, while the latter was only modestly affected. Even at high doses of M100907 (up to 9 mg/kg i.p.), spontaneous locomotion was not reduced below 40% of control. The selective dopamine D1 receptor antagonist (-)-[4aR,10aR]-1,2,3,4,4a,5,10,10a-octahydro-4-(4-chloro-2-methyl-phenyl)-1-methyl-benzo[g]quinoxaline-6-ol (SDZ PSD 958; 0.017, 0.15, 1.35 mg/kg i.p.) decreased both spontaneous and MK-801-induced locomotion with a slight preference for the latter; spontaneous locomotion was dose-dependently diminished to approx. 10% of controls (at 8 mg/kg i.p.). The dopamine D2 receptor antagonist raclopride ([(-)-(S)-3,5-dichloro-N-((1-ethyl-2-pyrrolidinyl) methyl)-6-methoxy-salicylamide tartrate]; 0.11, 0.33, 1.0 mg/kg i.p.) reduced both MK-801-induced and spontaneous locomotion to a similar extent. An orthogonal matrix exptl. design, and multiple regression, were used to evaluate the effects of several combinations of different doses of the **5-HT2A** receptor **antagonist** and the dopamine D1 receptor antagonist. No synergistic actions on redn. of spontaneous or MK-801-induced locomotion were detected between M100907 and SDZ PSD 958. If the hyperlocomotion elicited by acutely administered MK-801 is a valid model of at least some aspects of schizophrenia, these results indicate that the **5-HT2A** receptor **antagonist** M100907 will have efficacy in treating this condition.The lack of effect on spontaneous locomotion, suggests that M100907, compared to dopamine receptor antagonists, will be less prone to induce psychomotor side-effects. Ongoing clin. studies will hopefully give the answers in the near future.

CC 1-11 (Pharmacology)

IT **Hyperkinesia**
Schizophrenia
(MK-801-induced hyperlocomotion: differential effects of M100907, SDZ PSD 958 and raclopride)

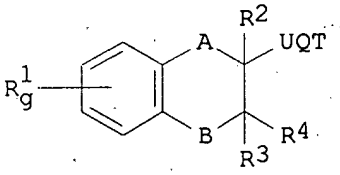
L9 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:921838 HCAPLUS
DOCUMENT NUMBER: 123:340154
TITLE: Preparation of aromatic bicyclic heterocyclic compounds as serotoninergic and dopaminergic receptor antagonists
INVENTOR(S): Kerrigan, Frank; Heal, David John; Martin, Keith Frank
PATENT ASSIGNEE(S): Boots Co. PLC, UK
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9507274	A1	19950316	WO 1994-EP2904	19940901
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
IN 179168	A	19970906	IN 1994-MA843	19940831
CA 2170056	AA	19950316	CA 1994-2170056	19940901
AU 9476928	A1	19950327	AU 1994-76928	19940901
AU 689802	B2	19980409		
EP 717739	A1	19960626	EP 1994-927531	19940901
EP 717739	B1	20000329		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CN 1133043	A	19961009	CN 1994-193808	19940901
CN 1052723	B	20000524		
BR 9407413	A	19961112	BR 1994-7413	19940901
JP 09502431	T2	19970311	JP 1994-508440	19940901
HU 75875	A2	19970528	HU 1996-552	19940901
RU 2136680	C1	19990910	RU 1996-113203	19940901
PL 178270	B1	20000331	PL 1994-313347	19940901
AT 191214	E	20000415	AT 1994-927531	19940901
ES 2144528	T3	20000616	ES 1994-927531	19940901
RO 116811	B1	20010629	RO 1996-406	19940901
IL 110844	A1	19991028	IL 1994-110844	19940902
ZA 9406798	A	19950406	ZA 1994-6798	19940905
BG 63272	B1	20010831	BG 1996-100388	19960229
FI 9601016	A	19960305	FI 1996-1016	19960305
NO 9600888	A	19960305	NO 1996-888	19960305
US 5767116	A	19980616	US 1996-605130	19960605

PRIORITY APPLN. INFO.: GB 1993-18431 A 19930906
WO 1994-EP2904 W 19940901

OTHER SOURCE(S): MARPAT 123:340154
GI



I

AB The title compds. [I; A, B = CH2, O; Q = N-contg. (un)substituted bridging group; R1 = halogen, (un)substituted alkyl, alkoxy, alkylthio, OH, acyloxy, CN, alkoxycarbonyl, (un)substituted carbamoyl, etc.; R2 = alkyl,

alkoxy; R3, R4 = H, alkyl; T = (un)substituted N-contg. heteroaryl, benzofuranyl, benzodioxanyl; U = (un)substituted alkylene; g = 0-4], useful as serotoninergic, adrenergic, and dopaminergic receptor antagonists, are prepd. and I-contg. formulations presented. Thus, N-(1,4-benzodioxan-2-ylmethyl)-1-[1-(3-chloropyrid-2-yl)piperid-4-yl]methylamine 1.4 hydrochloride , m.p. 251-253.degree., was prepd. from 2,3-dichloropyridine and demonstrated a Ki of 1.9 nM against rat brain-derived 5-HT1A receptors.

IC ICM C07D405-12
ICS C07D319-20; C07D405-06; C07D311-58; A61K031-335

CC 28-11 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27, 63

IT Drug dependence
Parkinsonism
Schizophrenia
(arom. bicyclic heterocycles for treatment of)

IT **Adrenergic antagonists**
(**.alpha.2**; arom. bicyclic heterocycles)

IT Brain, disease
(Gilles de la **Tourette**, arom. bicyclic heterocycles for treatment of)

IT **Neurotransmitter antagonists**
(**serotoninergic S1A**, arom. bicyclic heterocycles)

L9 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:683470 HCAPLUS
DOCUMENT NUMBER: 123:102617
TITLE: Blockade of phencyclidine-induced hyperlocomotion by clozapine and MDL 100,907 in rats reflects **antagonism** of **5-HT2A** receptors
AUTHOR(S): Maurel-Remy, S.; Bervoets, K.; Millan, Mark J.
CORPORATE SOURCE: Institut de Recherches Servier, Centre de Recherches de Croissy, 125 Chemin de Ronde, Croissy-sur-Seine, 78290, Fr.
SOURCE: European Journal of Pharmacology (1995), 280(2), R9-R11
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Whereas haloperidol more potently blocked the locomotion elicited by amphetamine (2.5 mg/kg i.p.) than that elicited by phencyclidine (PCP) (20.0 mg/kg s.c.), with ID50s of 0.04 and 0.09 mg/kg s.c., resp., clozapine more potently blocked the effect of PCP (0.04) than of amphetamine (8.8). Similarly, risperidone more potently blocked PCP (0.002) than amphetamine (0.2). In analogy to haloperidol, the selective dopamine D2 receptor antagonist, raclopride, antagonized amphetamine (0.16) more potently than PCP (0.8) whereas the selective **5-HT2A** receptor **antagonist**, [R(+)-**.alpha.**-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol] (MDL 100,907), only antagonized PCP (0.001) as compared to amphetamine (>10.0). The potency for inhibition of PCP correlated more highly to affinity at 5-HT2A ($r = 0.97$, $P<0.01$) than dopamine D2 (0.57, $P>0.05$) sites, while the potency for blockade of amphetamine correlated more highly with affinity at dopamine D2 (0.94, $P<0.01$) than at 5-HT2A sites (0.37, $P>0.05$). In conclusion, in contrast to amphetamine,

induction of locomotion by PCP is dependent upon functional **5-HT2A** receptors, **antagonism** of which by 'atypical' antipsychotics underlies their ability to inhibit PCP-induced locomotion.

CC 1-11 (Pharmacology)

IT **Hyperkinesia**
(5-HT2A receptors in phencyclidine-induced hyperlocomotion)

L9 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:266053 HCAPLUS
DOCUMENT NUMBER: 122:46350
TITLE: In vivo pharmacological profile of 9-hydroxyrisperidone, the major metabolite of the novel antipsychotic risperidone
AUTHOR(S): Megens, Anton A. H. P.; Awouters, Frans H. L.
CORPORATE SOURCE: Dep. Pharmacology, Jansen Res. Foundation, Beerse, Belg.
SOURCE: Drug Development Research (1994), 33(4), 399-412
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

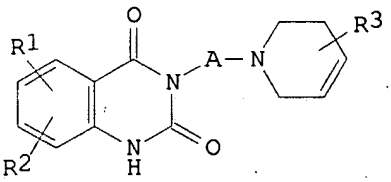
AB 9-Hydroxyrisperidone (9OH-risperidone) is the major metabolite of the new antipsychotic risperidone. 9OH-risperidone was compared with risperidone in a series of pharmacol. tests in rats; ritanserin and haloperidol were included as ref. compds. in tests for **5HT2** and D2 **antagonism**, resp. 9OH-risperidone closely resembled risperidone and showed similar effects at closely related doses (resp. s.c. [s.c.] ED5os in mg/kg in parentheses): **5HT2 antagonism**: reversal of tryptamine cyanosis (0.00059/0.0011), inhibition and blockade of tryptamine seizures (0.032/0.014 and 0.11/0.056), inhibition of tryptamine **tremors** (0.34/0.049), inhibition and blockade of apomorphine behavior (0.34/0.22 and 4.1/1.2), inhibition and blockade of amphetamine agitation (0.15/0.056 and 0.51/0.59) and oxygen consumption (0.049/0.016 and 0.17/0.064), behavioral disinhibition (0.069/0.031) and depression (4.6/4.7) in amphetaminized rats; histamine H1 antagonism: protection from compd. 48/80 lethality (0.018/0.014); .alpha.1-adrenoceptor antagonism: protection from norepinephrine lethality (0.17/0.074); .**alpha.2**-adrenoceptor **antagonism**: reversal of clonidine's antidiarrheal effect (0.29/0.67), reversal of xylazine loss of righting (16/2.4); and behavioral effects: slight and pronounced catalepsy (2.0/0.59 and 3.6/3.0), slight and pronounced palpebral ptosis (0.30/0.19 and 2.0/0.89), muscular hypotonia (4.7/3.6), hypothermia (4.1/2.0), inhibition of acetic acid writhing (1.2/0.34), and depression of motor activity (0.13/0.62 for vertical, 0.49/0.18 for horizontal, and 5.0/2.8 for total movements). Up to 10 mg/kg, both compds. were devoid of anti-muscarinic and anti-nicotinic activity, failed to affect the lethal effects of KCN, nitrogen, BaCl2 and ouabain, and did not block castor oil diarrhea. The acute oral LD50 values of the compds. were comparable. Both 9OH-risperidone and risperidone differed markedly from haloperidol as indicated by: (1) predominant central **5HT2 antagonism** (comparable to that of ritanserin); (2) high doses of catalepsy; (3) gradual depression of motor activity; (4) pronounced behavioral disinhibitory effects in amphetaminized rats; (5) inhibition of amphetamine-induced oxygen consumption preceding inhibition of amphetamine agitation. As metabolic conversion of risperidone to 9OH-risperidone does apparently not result in any marked change in activity profile, its major consequence seems to be a prolongation of duration of action.

CC 1-11 (Pharmacology)

L9 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:536122 HCAPLUS
DOCUMENT NUMBER: 115:136122
TITLE: Preparation of quinazoline derivatives as dopamine receptor agonists, serotonin (**5-HT**) receptor **antagonists**, or .alpha.1 receptor antagonist
INVENTOR(S): Norihiko, Shimazaki; Hitoshi, Yamazaki; Takumi, Yatabe; Hirokazu, Tanaka; Yoshikuni, Itoh; Masashi, Hashimoto
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 33 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 436157	A1	19910710	EP 1990-123876	19901212
EP 436157	B1	19950823		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ZA 9009951	A	19911030	ZA 1990-9951	19901211
AU 9068207	A1	19910704	AU 1990-68207	19901218
AU 635099	B2	19930311		
FI 9006425	A	19910703	FI 1990-6425	19901228
NO 9005620	A	19910703	NO 1990-5620	19901228
CA 2033363	AA	19910703	CA 1990-2033363	19901228
JP 05078349	A2	19930330	JP 1990-419312	19901228
CN 1053063	A	19910717	CN 1990-110247	19901231
HU 56089	A2	19910729	HU 1991-7	19910102
HU 208131	B	19930830		
PRIORITY APPLN. INFO.:			GB 1990-14	19900102
			GB 1990-25065	19901119

OTHER SOURCE(S): MARPAT 115:136122
GI



I

AB The title compds. [I; R1, R2 = H, halo, NO2, (un)protected NH2, OH, hydroxyalkyl or CO2H, HONH, alkyl, SONH2, SH, alkylthio, heterocyclylcarbonyl, heterocyclylalkyl; R3 = (un)substituted aryl; A = alkylene], useful as peripheral or central nervous system agents for treatment of dopamine-, 5-HT-, or .alpha.1 receptor-mediated diseases, e.g. hypertension, cardiovascular disorders such as angina pectoris and myocardial infarction, and **parkinsonism**, are prepd. Thus, a

mixt. of 0.52 g 2-amino-4-nitro-N-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzamide (prepn. given) and 0.43 g carbonyldiimidazole in THF was refluxed for 2 h to give 0.32 g I [R1 = 7-O2N, R2 = H, R3 = 4-Ph, A = (CH2)4] which (0.2 g) was refluxed with SnCl2 in EtOH to give 85 mg I (R1 = 7-HONH, R2, R3, A = unchanged) (II). II in vitro inhibited binding of [phenyl-4-3H]spiperone to dopamine receptor of homogenized rat brain tissue with an IC50 of 8.1 .times. 10-9 M.

IC ICM C07D401-06
ICS A61K031-415

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT **Neurotransmitter antagonists**
(**serotoninergic S2**, (tetrahydropyridinylalkyl)tetrahydroquinazolinediones)

IT **Adrenergic antagonists**
(.**alpha.2**-, (tetrahydropyridinylalkyl)tetrahydroquinazolinediones)

L9 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:74612 HCAPLUS
DOCUMENT NUMBER: 114:74612
TITLE: A novel in vivo test for drugs affecting central serotonergic and adrenergic systems
AUTHOR(S): Rawlow, Andrew; King, Roger G.
CORPORATE SOURCE: Dep. Pharmacol., Monash Univ., Clayton, 3168, Australia
SOURCE: European Journal of Pharmacology (1990), 191(3), 263-72
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In urethane anesthetized rats, **myoclonic** twitches of the anterior digastricus muscle were evoked by L-5-hydroxytryptophan (L-5-HTP, 50-100 mg/kg i.v.), the serotonin (5-HT) receptor agonist, quipazine (1-8 mg/kg i.v.) and the 5-HT releaser, fenfluramine (4-8 mg/kg i.v.). The effect of L-5-HTP or quipazine on the frequency of twitches was **inhibited** by the **5-HT** receptor **antagonist** cyproheptadine. Also L-DOPA (100 mg/kg i.p.) or the .alpha.1-adrenoceptor agonist, cirazoline (0.3-3 mg/kg i.v.) evoked twitches of the muscle which were inhibited by the .alpha.1-adrenoceptor antagonist, prazosin. In decerebrate, artificially respired rats, neither L-5-HTP nor L-DOPA evoked the twitches. The frequency of twitches evoked by fenfluramine but not by L-DOPA was increased by the .alpha.2-adrenoceptor agonist, clonidine (0.2 and 0.4 mg/kg i.v.); clonidine's effect was abolished by the .**alpha.2**-adrenoceptor **antagonist**, yohimbine. The .beta.2-adrenoceptor agonist, salbutamol (0.01-1 mg/kg i.v.) had no effect on fenfluramine-induced twitches. It is concluded that (1) activation of 5-HT receptors or .alpha.1-adrenoceptors in the brain of urethane-anesthetized rats evokes twitches of the anterior digastricus muscle, and (2) this prepn. can be utilized as a test to study the action of compds. on central 5-HT and adrenergic systems.

CC 1-1 (Pharmacology)

```
=> d que l27
L18      162726 SEA FILE=EMBASE ABB=ON  PLU=ON  MOTOR DYSFUNCTION+NT/CT
L19      203763 SEA FILE=EMBASE ABB=ON  PLU=ON  L18 OR MOVEMENT(2A)(DISORDER
                OR DISEASE) OR TREMOR? OR AKATHIS? OR ASTERIX? OR ATHETOS? OR
                CHOREOATH? OR TICS OR CHOREA? OR DYSTON? OR SPASTIC? OR
                RESTLESS LEGS OR HYPERKIN? OR HEMIBALL? OR MYOCLON? OR TARDIV?
                OR PARKINSON? OR RUBRAL? OR TOURETTE?
L21        1150 SEA FILE=EMBASE ABB=ON  PLU=ON  ALPHA 2 ADRENERGIC RECEPTOR
                BLOCKING AGENT/CT
L24         337 SEA FILE=EMBASE ABB=ON  PLU=ON  (SEROTONIN ANTAGONIST/CT OR
                (5HT? OR 5 HT?)(3A)(ANTAG? OR INHIB? OR BLOCK?)) AND (L21 OR
                (.ALPHA.2 OR ALPHA2 OR .ALPHA. 2 OR ALPHA 2)(3A)(ANTAG? OR
                INHIB? OR BLOCK?))
L25          21 SEA FILE=EMBASE ABB=ON  PLU=ON  L19 AND L24
L27          12 SEA FILE=EMBASE ABB=ON  PLU=ON  L25 AND (DT OR CB OR DRUG
                THERAP? OR DRUG(3A)COMBIN?)


=> dup rem l16 l27
FILE 'MEDLINE' ENTERED AT 15:34:12 ON 19 JUN 2003

FILE 'EMBASE' ENTERED AT 15:34:12 ON 19 JUN 2003
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PROCESSING COMPLETED FOR L16
PROCESSING COMPLETED FOR L27
L28          15 DUP REM L16 L27 (3 DUPLICATES REMOVED)

=> d ibib ab l28 1-15

L28  ANSWER 1 OF 15     MEDLINE
ACCESSION NUMBER:   2003216252     MEDLINE
DOCUMENT NUMBER:    22622048   PubMed ID: 12644843
TITLE:              The alpha 2-adrenoceptor
                    antagonist idazoxan reverses catalepsy induced by
                    haloperidol in rats independent of striatal dopamine
                    release: role of serotonergic mechanisms.
AUTHOR:             Invernizzi Roberto W; Garavaglia Claudio; Samanin Rosario
CORPORATE SOURCE:   Istituto di Ricerche Farmacologiche Mario Negri, Via
                    Eritrea 62, 20157 Milan, Italy.. rinvernizzi@marionegri.it
SOURCE:             NEUROPSYCHOPHARMACOLOGY, (2003 May) 28 (5) 872-9.
                    Journal code: 8904907. ISSN: 0893-133X.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200306
ENTRY DATE:         Entered STN: 20030513
                    Last Updated on STN: 20030612
                    Entered Medline: 20030611
AB   The alpha(2)-adrenoceptor antagonist
     idazoxan may improve motor symptoms in Parkinson's disease and
     experimental Parkinsonism. We studied the effect of idazoxan on
     haloperidol-induced catalepsy in rats, an animal model of the drug-induced
     extrapyramidal side effects in man. Catalepsy was induced by a
     subcutaneous (s.c.) injection of haloperidol (1 mg/kg) and measured by the
     bar test for a maximum of 5 min. At 3 h after haloperidol, rats were
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given 0.16-5.0 mg/kg s.c. idazoxan, and descent latency was measured 1 h later. Idazoxan potently reversed haloperidol-induced catalepsy with an ED(50) of 0.25 mg/kg. This effect was mimicked by the selective **alpha**(**2**)-adrenoceptor **antagonist** RS-15385-197 (0.3 and 1 mg/kg orally). We assessed how dopaminergic mechanisms were involved in the anticataleptic effect of idazoxan by studying its effect on dopamine (DA) release in the striatum, with the microdialysis technique in conscious rats. Idazoxan (0.3 and 2.5 mg/kg) had no effect on extracellular DA and did not modify the rise of extracellular DA induced by haloperidol, indicating that changes of striatal DA release were not involved in the reversal of catalepsy. The anticataleptic effect of 2.5 mg/kg idazoxan (haloperidol+vehicle 288+/-8 s, haloperidol+idazoxan 47+/-22 s) was attenuated in rats given an intraventricular injection of 150 microg of the serotonin (5-HT) neurotoxin 5,7-dihydroxytryptamine (haloperidol+vehicle 275+/-25 s, haloperidol+idazoxan 137+/-28 s). The **5-HT**(1A) receptor **antagonist** WAY100 635 (0.1 mg/kg s.c.) did not affect the anticataleptic effect of idazoxan. The results suggest that idazoxan reversed haloperidol-induced catalepsy by a mechanism involving **blockade** of **alpha**(**2**)-adrenoceptors and, at least in part, 5-HT neurons.

L28 ANSWER 2 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003041420 EMBASE
TITLE: Duloxetine pharmacology: Profile of a dual monoamine modulator.
AUTHOR: Karpa K.D.; Cavanaugh J.E.; Lakoski J.M.
CORPORATE SOURCE: Dr. J.M. Lakoski, Department of Pharmacology, Penn State College of Medicine, MC H078, 500 University Drive, Hershey, PA 17033-2390, United States. jml19@psu.edu
SOURCE: CNS Drug Reviews, (2002) 8/4 (361-376).
Refs: 65
ISSN: 1080-563X CODEN: CDREFB
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 028 Urology and Nephrology
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Dysregulation within central monoaminergic systems is believed to underlie the pathology of depression. Drugs that selectively inhibit the reuptake of central monoamines have been used clinically to alleviate symptoms of depressive illnesses. Duloxetine, a novel compound currently under investigation for the treatment of depression, binds selectively with high affinity to both norepinephrine (NE) and serotonin (5-HT) transporters and lacks affinity for monoamine receptors within the central nervous system. It has been suggested that dual inhibition of monoamine reuptake processes may offer advantages over other antidepressants currently in use. In preclinical studies, duloxetine mimics many physiologic effects of antidepressants. Consistent with other antidepressants, duloxetine, by acute administration, elevates extracellular monoamine levels, while by chronic administration it does not alter basal monoamine levels. Like the selective serotonin reuptake inhibitor, fluoxetine, by microiontophoretic application, duloxetine inhibits neuronal cell firing. However, in comparison with fluoxetine, duloxetine is a more potent serotonin reuptake inhibitor. Furthermore, in behavioral experiments, duloxetine attenuates

immobility in forced swim tests in animal models of depression to a greater extent than several other commonly used antidepressants. In a six-week open label uncontrolled study, duloxetine was evaluated in patients with a history of depression. Duloxetine was effective in treating depression as determined by marked reduction in Hamilton Depression Rating scores. Adverse effects reported during duloxetine treatment were minor and similar to those of other antidepressants. In an eight-week multicenter, double-blind, placebo-controlled study in patients with a major depressive disorder, duloxetine was effective as an antidepressant, particularly in patients with greater symptom severity. Only limited data are available regarding the pharmacokinetic profile of duloxetine in humans, although a half-life of 10 to 15 h has been reported. Studies conducted in healthy human subjects confirm the preclinical profile of duloxetine as an **inhibitor** of **5-HT** and NE reuptake. Taken together, existing data suggest that duloxetine is a novel and effective antidepressant.

L28 ANSWER 3 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002043612 EMBASE
TITLE: The pharmacology of human working memory.
AUTHOR: Ellis K.A.; Nathan P.J.
CORPORATE SOURCE: Dr. P.J. Nathan, Neuropharmacology Laboratory, Brain Sciences Institute, Swinburne University of Technology, 400 Burwood Road, Hawthorn, Vic. 3122, Australia. pnathan@bsi.swin.edu.au
SOURCE: International Journal of Neuropsychopharmacology, (2001) 4/3 (299-313).
Refs: 103
ISSN: 1461-1457 CODEN: IJNUFB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Experimental studies conducted primarily on non-human primates have begun to address the anatomical and neurochemical correlates of working memory. There is an associated growing body of experimental literature investigating whether modulating key neurotransmitters can facilitate working memory in humans. This paper reviews evidence that acute modulation of dopamine in particular, but also noradrenaline, acetylcholine and serotonin may influence working-memory performance in humans. Differences in neurochemical specificity with regard to stages of working memory, type of working memory (spatial or non-spatial) and cortical effects are also discussed. This evidence has contributed to neuropharmacological understanding of working memory in humans. The important therapeutic consequences of a better understanding of facilitation of working memory is discussed in reference to schizophrenia, **Parkinson**'s disease and Alzheimer's disease.

L28 ANSWER 4 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000246364 EMBASE
TITLE: In-vivo assessment of 5-HT(2A) and **5-HT** (2C) **antagonistic** properties of newer

antipsychotics.
AUTHOR: Sanchez C.; Arnt J.
CORPORATE SOURCE: C. Sanchez, Neuropharmacology Department, H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark. CS@lundbeck.com
SOURCE: Behavioural Pharmacology, (2000) 11/3-4 (291-298).
Refs: 30
ISSN: 0955-8810 CODEN: BPHAEL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
032 Psychiatry
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The effects of serotonin (5-HT) receptor ligands on the MK 212 (6-chloro-2[1-piperazinyl]pyrazine) discriminative stimulus and quipazine-induced head twitches were studied in rats. 5-HT(1A) (8-OH-DPAT) and preferential 5-HT(2A) (DOI) receptor agonists did not generalize to the discriminative stimulus. The **5-HT**(2B/2C)-receptor **antagonist**, SB 206553 (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-f]indole), and the **5-HT**(2A/2C)-receptor **antagonist**, ritanserin, acted as potent **antagonists**, whereas the **5-HT**(2A)-receptor **antagonist**, MDL 100.151 ([(.+-.)-.**alpha**.-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4- piperidine-methanol), produced minor and inconsistent inhibition. SB 206553 was a weak antagonist against quipazine-induced head twitches, whereas MDL 100.151 and ritanserin were potent antagonists. This suggests that the MK 212 discriminative stimulus is mediated by 5-HT(2C) receptors, while quipazine-induced head twitches are mediated primarily by 5-HT(2A) receptors. The effects on quipazine-induced head twitches were comparable to previously published effects on the DOI discriminative stimulus. 5-HT(2A)- and **5-HT**(2C)-receptor **antagonistic** potencies of clozapine, olanzapine, risperidone, sertindole and ziprasidone were compared in the same models. Clozapine showed similar potencies in both models, while sertindole, olanzapine and risperidone inhibited quipazine-induced effects more potently than the MK 212 discriminative stimulus. Ziprasidone exerted a minor preference for 5-HT(2A)- compared to 5-HT(2C)-receptor-mediated effects. The ratio between in vivo **inhibitory** potencies at **5-HT**(2A) and 5-HT(2C) receptors did not correlate with corresponding ratios from in-vitro affinity and ex-vivo occupancy studies in the literature. (C) 2000 Lippincott Williams and Wilkins.

L28 ANSWER 5 OF 15 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999043311 MEDLINE
DOCUMENT NUMBER: 99043311 PubMed ID: 9827609
TITLE: Adjuncts to dopamine replacement: a pragmatic approach to reducing the problem of dyskinesia in **Parkinson**'s disease.
AUTHOR: Brotchie J M
CORPORATE SOURCE: Division of Neuroscience, School of Biological Sciences, University of Manchester, UK.
SOURCE: MOVEMENT DISORDERS, (1998 Nov) 13 (6) 871-6. Ref: 14
Journal code: 8610688. ISSN: 0885-3185.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990301
Last Updated on STN: 19990301
Entered Medline: 19990217

AB Dyskinesias following long-term dopamine replacement therapy are a major limitation of current treatments for **Parkinson**'s disease. Recently, attention has been focused on the concept of using non-dopaminergic adjuncts to currently available therapies in an attempt to reduce the problem of dyskinesia. Thus, an enhanced understanding of the neural mechanisms underlying dyskinetic symptoms has led to the realization that it might be possible to manipulate non-dopaminergic systems and reduce dyskinesia without compromising the anti-**parkinsonian** efficacy of drugs such as L-dopa. This article discusses how non-dopaminergic manipulations could reverse the abnormalities in basal ganglia circuitry responsible for generating dyskinesia. It is proposed that potential anti-dyskinetic drugs might include glutamate (NMDA) receptor antagonists, opioid receptor antagonists, cannabinoid receptor agonists or **antagonists**, **alpha2** adrenergic receptor **antagonists**, and **5-HT**-enhancing agents.

L28 ANSWER 6 OF 15 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998292485 MEDLINE
DOCUMENT NUMBER: 98292485 PubMed ID: 9628768
TITLE: Characterization of enhanced behavioral responses to L-DOPA following repeated administration in the 6-hydroxydopamine-lesioned rat model of **Parkinson**'s disease.
AUTHOR: Henry B; Crossman A R; Brotchie J M
CORPORATE SOURCE: Division of Neuroscience, School of Biological Sciences, University of Manchester, 1.124 Stopford Building, Manchester, M13 9PT, United Kingdom.
SOURCE: EXPERIMENTAL NEUROLOGY, (1998 Jun) 151 (2) 334-42.
Journal code: 0370712. ISSN: 0014-4886.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 20000303
Entered Medline: 19980709

AB Long-term treatment of **Parkinson**'s disease with dopamine-replacing agents such as L-3,4-dihydroxyphenylalanine (L-DOPA) is compromised by many side-effects, most notably involuntary movements, L-DOPA-induced dyskinesia. Acute challenge with dopamine-replacing drugs elicits a rotational response in the 6-hydroxydopamine (6-OHDA)-lesioned rat model of **Parkinson**'s disease. This rotation is contraversive to the lesion and is considered to represent an antiparkinsonian effect. More recently, it has become clear that the rotational response shows plasticity and that repeated L-DOPA or apomorphine therapy is accompanied by a marked enhancement in this

response. In this study, we demonstrate that the enhanced behavioral response to repeated dopamine-replacement therapy seen in the 6-OHDA-lesioned rat has pharmacological characteristics similar to L-DOPA-induced dyskinesia seen in MPTP-lesioned primates and man. Thus, the magnitude and rate of development of the enhanced response to L-DOPA treatment is related to both the number of doses and the size of the dose of L-DOPA administered. In contrast, de novo administration of dopaminergic drugs that are associated with a lower incidence of dyskinesia, e.g., bromocriptine or lisuride, does not lead to an enhanced behavioral response following repeated treatment. However, following a single "priming" administration of apomorphine, the rotational response elicited by subsequent bromocriptine administrations is enhanced with repeated treatment. Once established, the enhanced behavioral response to repeated L-DOPA-administration (6.5 mg/kg, twice daily) can, like L-DOPA-induced dyskinesia in man and MPTP-treated monkeys, be selectively reduced by coadministration of L-DOPA with the **alpha2**-adrenergic receptor **antagonist** yohimbine (10 mg/kg, -95%), the **5-HT** uptake **inhibitor** 5-MDOT (2 mg/kg, -90%), or the beta-adrenergic receptor antagonist propranalol (10 mg/kg, -35%). While these rats do not exhibit symptoms of dyskinesia per se, this rodent model does exhibit behaviors, the underlying mechanism of which is likely to be similar to that underlying L-DOPA-induced dyskinesia and may prove useful in studying the molecular and cellular mechanisms of L-DOPA-induced dyskinesia in **Parkinson**'s disease.

L28 ANSWER 7 OF 15 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999081105 MEDLINE
DOCUMENT NUMBER: 99081105 PubMed ID: 9865507
TITLE: Head and whole-body jerking in guinea pigs are differentially modulated by 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists**.
AUTHOR: Nielsen C K
CORPORATE SOURCE: Pharmacological Research, H. Lundbeck A/S, Copenhagen, Denmark.. ckn@lundbeck.com
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1998 Nov 20) 361 (2-3) 185-90.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 20030118
Entered Medline: 19990222

AB The present study examined the role of 5-hydroxytryptamine 5-HT receptor subtypes on 5-hydroxytryptamine- (5-HT-) mediated **myoclonus** in guinea pigs, evaluating head and whole-body jerking as two distinct behavioural responses. **Myoclonus** was induced by the 5-HT precursor L-5-hydroxytryptophan (L-5-HTP) and the non-selective 5-HT1A/1B/5-HT2 receptor agonist 5-methoxy-N,N-dimethyl-tryptamine (5-MeODMT). The selective **5-HT1A** receptor **antagonist** WAY100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cycloh exanecarboxamide trihydrochloride) inhibited both head and whole-body jerking. The selective **5-HT1B**/1D receptor **antagonist**

GR127935 (N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1 ,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide hemifumarate) only inhibited whole-body jerking, which resulted in unmasked head jerking. Co-administration of GR127935 and the selective **5-HT2A** receptor **antagonist** MDL100.151 ((+/-)-**alpha**-(**2**,3-dimethoxyphenyl)-1-[-2-(4-fluorphenyl)ethyl]-4-++piperidinmethanol) caused a complete inhibition of whole-body as well as head jerking. MDL100.151 had only limited effect on **myoclonic** jerking when given alone. The **inhibitory** effects of the **5-HT** receptor **antagonists** on either L-**5-HTP**- or 5-MeODMT-induced **myoclonus** were found to be very similar. These data confirm a role for the 5-HT1A and 5-HT1B/1D receptors and suggest a role for 5-HT2A receptors in mediating **myoclonus** in guinea pigs. Moreover, the study shows that by considering head and whole-body jerking as two pharmacologically distinct behavioural responses, subtype specific 5-HT1A, 5-HT1B/1D and **5-HT2A** receptor **antagonists** can be distinguished.

L28 ANSWER 8 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97101330 EMBASE
DOCUMENT NUMBER: 1997101330
TITLE: .**alpha**.**2**-Adrenoceptor **antagonists** reverse the **5-HT2** receptor **antagonist** suppression of head-twitch behavior in mice.
AUTHOR: Matsumoto K.; Mizowaki M.; Thongpraditchote S.; Murakami Y.; Watanabe H.
CORPORATE SOURCE: H. Watanabe, Department of Pharmacology, Research Institute for Wakan-Yaku, Toyama Medical/Pharmaceutical Univ., 2630 Sugitani, 930-01 Toyama, Japan
SOURCE: Pharmacology Biochemistry and Behavior, (1997) 56/3 (417-422).
Refs: 24
ISSN: 0091-3057 CODEN: PBBHAU
PUBLISHER IDENT.: S 0091-3057(96)00223-7
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The .alpha.2-adrenoceptor agonist clonidine, as well as **5-HT** receptor **antagonists**, reportedly suppress **5-HT2** receptor-mediated head-twitch behavior. We investigated the effect of .**alpha**.**2**-adrenoceptor **antagonists** on the suppressive action of **5-HT2** receptor **antagonists** in mice pretreated with the noradrenaline toxin 6-hydroxydopamine (6-OHDA) or the **5-HT** synthesis **inhibitor** p-chlorophenylalanine (p-CPA). In normal mice, idazoxan (0.08-0.2 mg/kg, IP) or yohimbine (0.2-2.0 mg/kg, IP), both .**alpha**.2-adrenoceptor **antagonists**, had no effect on the head-twitch response caused by 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT; 16 mg/kg, IP), but idazoxan significantly enhanced the response at 0.5 mg/kg. On the other hand, these .**alpha**.**2**-adrenoceptor **antagonists**, at doses that had no effect on the basal number of head-twitches (idazoxan 0.2 mg/kg and yohimbine 0.5

mg/kg), significantly attenuated not only the suppressive effect of clonidine (0.01 mg/kg, IP) on head-twitch response but also that of the **5-HT2** receptor **antagonist** ritanserin (0.03 mg/kg, IP). Moreover, idazoxan (0.2 mg/kg) also significantly reversed the inhibition by 0.01 mg/kg (IP) ketanserin, a selective **5-HT2** receptor **antagonist**. Pretreatment with 6-OHDA plus nomifensine but not with p-CPA significantly attenuated the effect of idazoxan (0.2-0.5 mg/kg) on the ritanserin inhibition of the head-twitch response. Prazosin, an .alpha.1-adrenoceptor antagonist, dose-dependently suppressed the response, and the effect of prazosin (1.25 mg/kg) was significantly attenuated by 0.5 mg/kg idazoxan. These results indicate that endogenous noradrenaline is involved in the apparent **antagonistic** interaction between selective **.alpha.** 2-adrenoceptor **antagonists** and **5-HT2** receptor **antagonists** in the head-twitch response, and suggest that noradrenaline stimulation of .alpha.1-adrenoceptors may be involved in this apparent antagonism.

L28 ANSWER 9 OF 15 MEDLINE
ACCESSION NUMBER: 1998034295 MEDLINE
DOCUMENT NUMBER: 98034295 PubMed ID: 9369362
TITLE: MK-801-induced hyperlocomotion: differential effects of M100907, SDZ PSD 958 and raclopride.
AUTHOR: Martin P; Waters N; Waters S; Carlsson A; Carlsson M L
CORPORATE SOURCE: Department of Pharmacology, Goteborg University, Sweden.. peter.martin@pharm.gu.se
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1997 Sep 24) 335 (2-3) 107-16.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 20000303
Entered Medline: 19971222

AB The influence of three selective monoamine receptor antagonists on spontaneous locomotion and on the hyperlocomotion induced by the un-competitive N-methyl-D-aspartate (NMDA) receptor antagonist [+]-5-methyl-10,11-dihydro-5H-dibenzo-[a,d]-cyclohepten-5,10-imine hydrogen maleate (MK-801; dizocilpine) was investigated. The selective and potent 5-hydroxytryptamine (**5-HT**)2A receptor **antagonist** R(+)-**alpha**-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol (MDL100,907; M100907) displayed a clear-cut selectivity for reduction of MK-801-induced as compared to spontaneous locomotion, in that the former was dose-dependently (0.001, 0.01, 0.1 mg/kg i.p.) blocked and even totally abolished by the highest dose, while the latter was only modestly affected. Even at high doses of M100907 (up to 9 mg/kg i.p.), spontaneous locomotion was not reduced below 40% of control. The selective dopamine D1 receptor antagonist (-)-[4aR, 10 aR]-1,2,3,4,4a,5,10,10a-octahydro-4-(4-chloro-2-methyl-phenyl)-1-methyl- benzo[g]quinoxaline-6-ol (SDZ PSD 958; 0.017, 0.15, 1.35 mg/kg i.p.) decreased both spontaneous and MK-801-induced locomotion with a slight preference for the latter; spontaneous locomotion was dose-dependently diminished to approx. 10% of controls (at 8 mg/kg i.p.). The dopamine D2 receptor antagonist

raclopride ([(-)-(S)-3,5-dichloro-N-((1-ethyl-2-pyrrolidinyl) methyl)-6-methoxy-salicylamide tartrate]; 0.11, 0.33, 1.0 mg/kg i.p.) reduced both MK-801-induced and spontaneous locomotion to a similar extent. An orthogonal matrix experimental design, and multiple regression, were used to evaluate the effects of several combinations of different doses of the **5-HT2A** receptor **antagonist** and the dopamine D1 receptor antagonist. No synergistic actions on reduction of spontaneous or MK-801-induced locomotion were detected between M100907 and SDZ PSD 958. If the hyperlocomotion elicited by acutely administered MK-801 is a valid model of at least some aspects of schizophrenia, these results indicate that the **5-HT2A** receptor **antagonist** M100907 will have efficacy in treating this condition.The lack of effect on spontaneous locomotion, suggests that M100907, compared to dopamine receptor antagonists, will be less prone to induce psychomotor side-effects. Ongoing clinical studies will hopefully give the answers in the near future.

L28 ANSWER 10 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96158818 EMBASE
DOCUMENT NUMBER: 1996158818
TITLE: Mirtazapine. A review of its pharmacology and therapeutic potential in the management of major depression.
AUTHOR: Davis R.; Wilde M.I.
CORPORATE SOURCE: Adis International Limited, 41 Centorian Drive,Mairangi Bay, Auckland 10, New Zealand
SOURCE: CNS Drugs, (1996) 5/5 (389-402).
ISSN: 1172-7047 CODEN: CNDREF
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Mirtazapine is a tetracyclic antidepressant with a novel mechanism of action; it increases noradrenergic and serotonergic neurotransmission via **blockade** of central **alpha 2**-adrenergic auto- and heteroreceptors. The increased release of serotonin (5-hydroxytryptamine; 5-HT) stimulates serotonin 5-HT1 receptors because mirtazapine directly **blocks 5-HT2** and **5-HT3** receptors. The enhancement of both noradrenergic- and 5-HT1 receptor-mediated neurotransmission is thought to be responsible for the antidepressant activity of mirtazapine. In short term (5 to 6 weeks) clinical trials in patients with depression, mirtazapine produces clinical improvements significantly superior to those of placebo, similar to those of tricyclic antidepressants (TCAs) [amitriptyline, clomipramine and doxepin] and possibly superior to those of trazodone. Short term clinical tolerability data suggest that mirtazapine produces fewer anticholinergic-, adrenergic- and serotonergic-related adverse events than TCAs. In rare cases, mirtazapine, in common with many antidepressants, was associated with potentially serious changes in haematological parameters (e.g. agranulocytosis and neutropenia). The drug appears to be safe in overdose and possesses a very low propensity for inducing seizures. Comparisons with other classes of antidepressants are needed to determine the relative position of mirtazapine in clinical practice. However, preliminary data indicate that mirtazapine, with its novel mechanism of

action, is a promising addition to currently available options for the treatment of depression.

L28 ANSWER 11 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96375422 EMBASE
DOCUMENT NUMBER: 1996375422
TITLE: The stimulatory and inhibitory components of cocaine's actions on the 5-HTP-induced 5-HT(2A) receptor response.
AUTHOR: Darmani N.A.; Reeves S.L.
CORPORATE SOURCE: Department of Pharmacology, Kirksville College, Osteopathic Medicine, 800 West Jefferson Street,Kirksville, MO 63501, United States
SOURCE: Pharmacology Biochemistry and Behavior, (1996) 55/3 (387-396).
ISSN: 0091-3057 CODEN: PBBHAU
PUBLISHER IDENT.: S 0091-3057(96)00108-6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
040 Drug Dependence, Alcohol Abuse and Alcoholism
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Previously we have shown that cocaine attenuates the 5-HT(2A) receptor-mediated head-twitch response (HTR) in mice produced by the 5-HT(2A/C) direct agonist (.+-.)-1(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). This inhibition appears to be due to cocaine-induced indirect stimulation of the **inhibitory** serotonergic **5-HT**(1A) and noradrenergic .**alpha.2** receptors via the **inhibition** of reuptake of synaptic serotonin (5-HT) and norepinephrine (NE), respectively. In the present study, we investigated the effects of cocaine, its phenyltropane analogue WIN 35428, and the selective 5-HT (sertraline), NE (nisoxetine) and dopamine (DA) (GBR 12935) reuptake inhibitors on the 5-hydroxytryptophan (5-(HTP)-induced HTR. We utilized two experimental protocols where cocaine or the cited drugs were administered either after (protocol 1) or prior (protocol 2) to 5-HTP injection. Cocaine in both protocols produced a dose-dependent enhancement in the 5-HTP-induced HTR (ED50 4.68 .+-. 1.21 and 3.55 .+-. 1.31, respectively). Sertraline was more potent (ED50 2.64 .+-. 1.1 and 2.1 .+-. 1.54, respectively) in enhancing the induced behavior and dose by dose produced greater (3 to 10 times) HTRs than cocaine. On the other hand, nisoxetine dose dependently and completely attenuated the induced behavior (ID50 3.33 .+-. 1.32 and 1.72 .+-. 1.34, respectively), whereas GBR 12935 only at high doses (ID50 15.34 .+-. 1.52 and 11.91 .+-. 1.3, respectively) decreased the induced response. The inability of cocaine to induce as many HTRs as sertraline appears to lie in its ability to also indirectly stimulate the **inhibitory 5-HT**(1A) and .alpha.2 receptors because the stimulant caused greater enhancement in the 5-HTP-induced HTRs in the presence of their corresponding antagonists [S(-)-UH 301 and yohimbine, respectively]. WIN 35428 was more potent (ED50 2.87 .+-. 1.3 and 1.79 .+-. 1.1 for protocols 1 and 2, respectively) in stimulating the 5-HTP-induced HTR and produced a bell-shaped dose-response curve. The results indicate that cocaine enhances the 5-HTP-induced HTR via the **inhibition** of synaptic **5-HT** reuptake. The stimulant also simultaneously attenuates the induced behavior by indirect simulation of the serotonergic 5-HT(1A) and

noradrenergic **.alpha.2** receptors via **inhibition** of reuptake of the corresponding monoamines.

L28 ANSWER 12 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95075095 EMBASE
DOCUMENT NUMBER: 1995075095
TITLE: In vivo pharmacological profile of 9-hydroxyrisperidone, the major metabolite of the novel antipsychotic risperidone.
AUTHOR: Megens A.A.H.P.; Awouters F.H.L.
CORPORATE SOURCE: Department of Pharmacology, Janssen Research Foundation,2340 Beerse, Belgium
SOURCE: Drug Development Research, (1994) 33/4 (399-412).
ISSN: 0272-4391 CODEN: DDREDK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
032 Psychiatry
040 Drug Dependence, Alcohol Abuse and Alcoholism
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 9-Hydroxyrisperidone (9OH-risperidone) is the major metabolite of the new antipsychotic risperidone. 9OH-risperidone was compared with risperidone in a series of pharmacological tests in rats; ritanserin and haloperidol were included as reference compounds in tests for **5HT2** and D2 **antagonism**, respectively. 9OH-risperidone closely resembled risperidone and showed similar effects at closely related doses (respective subcutaneous [sc] ED50s in mg/kg in parentheses): **5HT2 antagonism**: reversal of tryptamine cyanosis (0.00059/0.0011), inhibition and blockade of tryptamine seizures (0.03210.014 and 0.1110.056), inhibition of tryptamine **tremors** (0.34/ 0.049), inhibition and blockade of mescaline head twitches (0.056/0.037 and 0.098/0.049); D2 antagonism: inhibition and blockade of apomorphine behavior (0.34/0.22 and 4.1/1.2), inhibition and blockade of amphetamine agitation (0.15/0.056 and 0.51/0.59) and oxygen consumption (0.049/0.016 and 0.17/0.064); behavioral disinhibition (0.069/0.031) and depression (4.6/4.7) in amphetaminized rats; histamine H1 antagonism: protection from compound 48/80 lethality (0.018/0.014); .alpha.1-adrenoceptor antagonism: protection from norepinephrine lethality (0.17/0.074); **.alpha.** 2-adrenoceptor **antagonism**: reversal of clonidine/s antidiarrheal effect (0.29/0.67), reversal of xylazine loss of righting (16/2.4); and behavioral effects: slight and pronounced catalepsy (2.0/0.59 and 3.6/3.0), slight and pronounced palpebral ptosis (0.30/0.19 and 2.0/0.89), muscular hypotonia (4.7/3.6), hypothermia (4.1/2.0), inhibition of acetic acid writhing (1.2/0.34), and depression of motor activity (0.13/0.062 for vertical, 0.49/0.18 for horizontal, and 5.0/2.8 for total movements). Up to 10 mg/kg, both compounds were devoid of anti-muscarinic and anti-nicotinic activity, failed to affect the lethal effects of KCN, nitrogen, BaCl2 and ouabain, and did not block castor oil diarrhea. The acute oral LD50 values of the compounds were comparable. Both 9OH-risperidone and risperidone differed markedly from haloperidol as indicated by: (1) predominant central **5HT2 antagonism** (comparable to that of ritanserin); (2) high doses of catalepsy; (3) gradual depression of motor activity; (4) pronounced behavioral disinhibitory effects in amphetaminized rats; (5) inhibition of

amphetamine-induced oxygen consumption preceding inhibition of amphetamine agitation. As metabolic conversion of risperidone to 9OH-risperidone does apparently not result in any marked change in activity profile, its major consequence seems to be a prolongation of duration of action.

L28 ANSWER 13 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94284713 EMBASE
DOCUMENT NUMBER: 1994284713
TITLE: Pharmacotherapy of the depressed patient with cardiovascular and/or cerebrovascular illness.
AUTHOR: Lane R.M.; Sweeney M.; Henry J.A.
CORPORATE SOURCE: International Pharmaceuticals Group, Pfizer Inc, 235 East 42nd Street,New York, NY 10017-5755, United States
SOURCE: British Journal of Clinical Practice, (1994) 48/5 (256-262).
ISSN: 0007-0947 CODEN: BJCPAT
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cardiovascular and cerebrovascular disease are associated with a high incidence of depressive disorder. Despite this high level of co-morbidity, depressive disorders appear to go largely unrecognised and remain untreated. This may have serious consequences, as concomitant depression worsens the prognosis in patients with cardiovascular or cerebrovascular disease, increases medical costs, and delays return to work. Treatment with traditional tricyclic antidepressants is difficult in these patients because of the known cardiac effects. The favourable side-effect profiles of the **5-HT** reuptake **inhibitors** suggest that they may offer therapeutic advantages, as they have little or no effect on cardiac conduction, do not cause orthostatic hypotension, and lack serious sequelae in overdose. The pharmacological profiles and the reduced potential of these newer antidepressant drugs to cause drug interaction show important differences that may be of clinical relevance in this patient population.

L28 ANSWER 14 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93165229 EMBASE
DOCUMENT NUMBER: 1993165229
TITLE: Role of the **inhibitory** adrenergic **.alpha .2** and serotoninergic 5-HT(1A) components of cocaine's actions on the DOI-induced head-twitch response in 5-HT2-receptor supersensitive mice.
AUTHOR: Darmani N.A.
CORPORATE SOURCE: Department of Pharmacology, Kirskville Coll. of Osteopathic Med.,Kirskville, MO 63501, United States
SOURCE: Pharmacology Biochemistry and Behavior, (1993) 45/2 (269-274).
ISSN: 0091-3057 CODEN: PBBHAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 040 Drug Dependence, Alcohol Abuse and Alcoholism

030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB It was recently reported that acute cocaine pretreatment can reduce the (.+-.)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced 5-hydroxytryptamine2 (5-HT2)-receptor mediated head-twitch response (HTR) in mice via indirect stimulation of adrenergic .alpha.2- and serotonergic 5-HT(1A)-receptors. The aim of the present investigation was to determine whether cocaine can alter the DOI-induced HTR in 5-HT2-receptor supersensitive mice. Supersensitivity was induced by a single injection of DOI 48 h prior to experimentation. These supersensitive mice exhibited a greater frequency of HTR to a challenge dose of DOI 48 h after its initial administration. Cocaine pretreatment dose-dependently reduced the DOI-induced HTR in the supersensitive mice. The stimulant was approximately four times more potent in the 5-HT2-receptor supersensitive mice relative to its reported effects in normal mice. Receptor blockade studies with yohimbine and alprenolol revealed that both of the inhibitory components of cocaine's actions (i.e., adrenergic .alpha.2- and serotonergic 5-HT(1A)-receptor effects, respectively) were more efficient in reducing the DOI-induced HTR in supersensitive mice compared to normosensitive animals. The present results further support the previously suggested hypothesis that acute cocaine administration **inhibits** the **5-HT2** receptor function by increasing the synaptic concentration of norepinephrine and serotonin via inhibition of their uptake and therefore indirectly stimulating the respective **inhibitory** adrenergic **.alpha.2**- and serotonergic 5-HT(1A)-receptors.

L28 ANSWER 15 OF 15 MEDLINE
ACCESSION NUMBER: 91200133 MEDLINE
DOCUMENT NUMBER: 91200133 PubMed ID: 1982266
TITLE: A novel in vivo test for drugs affecting central serotonergic and adrenergic systems.
AUTHOR: Rawlow A; King R G
CORPORATE SOURCE: Department of Pharmacology, Monash University, Clayton, Victoria, Australia.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1990 Dec 4) 191 (3) 263-72.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 19910607
Last Updated on STN: 19950206
Entered Medline: 19910523

dupl.

AB In urethane-anaesthetized rats, **myoclonic** twitches of the anterior digastricus muscle were evoked by L-5-hydroxy-tryptophan (L-5-HTP, 50-100 mg/kg iv.), the serotonin (5-HT) receptor agonist, quipazine (1-8 mg/kg i.v.) and the 5-HT releaser, fenfluramine (4-8 mg/kg i.v.). The effect of L-5-HTP or quipazine on the frequency of twitches was **inhibited** by the **5-HT** receptor **antagonist** cyproheptadine. Also L-DOPA (100 mg/kg i.p.) or the alpha 1-adrenoceptor agonist, cirazoline (0.3-3 mg/kg i.v.) evoked twitches of the muscle which were inhibited by the alpha 1-adrenoceptor

antagonist, prazosin. In decerebrate, artificially respired rats, neither L-5-HTP nor L-DOPA evoked the twitches. The frequency of twitches evoked by fenfluramine but not by L-DOPA was increased by the alpha 2-adrenoceptor agonist, clonidine (0.2 and 0.4 mg/kg i.v.); clonidine's effect was abolished by the **alpha 2**-adrenoceptor **antagonist**, yohimbine. The beta 2-adrenoceptor agonist, salbutamol (0.01-1 mg/kg i.v.) had no effect on fenfluramine-induced twitches. It is concluded that (1) activation of 5-HT receptors or alpha 1-adrenoceptors in the brain of urethane-anaesthetized rats evokes twitches of the anterior digastricus muscle, and (2) this preparation can be utilized as a test to study the action of compounds on central 5-HT and adrenergic systems.

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